HEALTH LAW, ETHICS, AND HUMAN RIGHTS

Ethical Considerations in Studying Drug Safety — The Institute of Medicine Report

Michelle M. Mello, J.D., Ph.D., Steven N. Goodman, M.D., M.H.S., Ph.D., and Ruth R. Faden, Ph.D., M.P.H.

The tumult arising from revelations of serious safety risks associated with widely prescribed drugs, including rosiglitazone (Avandia, GlaxoSmithKline), rofecoxib (Vioxx, Merck), and celecoxib (Celebrex, Pfizer), has led to widespread recognition that improvement is needed in our national system of ensuring drug safety. Notwithstanding federal legislation in 2007 that strengthened the authority of the Food and Drug Administration (FDA) in the postmarketing period,[1] critical weaknesses in the national system persist.

Central to these weaknesses are dilemmas surrounding not only the science but also the ethics of drug-safety research,[2] many of which came to the fore in the heated public debate about the Thiazolidinedione Intervention with Vitamin D Evaluation (TIDE) trial, which compared the cardiovascular outcomes of long-term treatment with rosiglitazone with those of pioglitazone (Actos, Takeda) in patients with type 2 diabetes.[3] At the request of the FDA, an Institute of Medicine (IOM) committee, on which we served, was convened to examine the ethics and science of FDA-required postmarketing safety research. In this article, we review the key ethics findings from the committee's May 1, 2012, report[4] and offer some reflections on the challenges ahead.

LESSONS FROM THE TIDE TRIAL

In May 2008, the FDA ordered the manufacturer of rosiglitazone, GlaxoSmithKline, to conduct a trial in response to evidence from meta-analyses that rosiglitazone was associated with a higher risk of myocardial infarction and death from cardiovascular causes than placebo or medications that were not based on nonthiazolidinedione comparators.[5,6] Other studies suggested that pioglitazone, an alternative thiazolidinedione, was not associated with such risks.[7,8] Before enrollment began, some argued that the evidence of the inferior safety of rosiglitazone was strong enough to make the trial ethically unjustifiable. Two FDA epidemiologists wrote in a 2008 memorandum that a head-to-head trial "would be unethical and exploitative" and that even a robust informed-consent process could not overcome the problem.[9] This was not the consensus FDA view, which was that the uncertainty regarding the cardiovascular risks associated with rosiglitazone, as well as those associated with pioglitazone, was sufficient to justify a trial.[10]

These concerns triggered a February 2010 letter from members of Congress to the FDA demanding a justification for the trial and alleging that the consent form did not provide adequate risk information.[11] In response, FDA Commissioner Margaret Hamburg expanded the FDA investigation of the safety of rosiglitazone, obtained advice from an FDA advisory committee, and asked the IOM to convene our committee.[6] Although the FDA advisory committee recommended that the TIDE trial be continued if rosiglitazone was permitted to remain on the market, in September 2010, the FDA halted the trial and placed stringent new restrictions on the availability of rosiglitazone.[12,13]

The TIDE experience made the FDA appreciate the need for greater attention to the ethics of postmarketing research. First, it posed questions about what standard of evidence about drug risk justifies a decision by the FDA to require postmarketing research, particularly randomized trials, as well as what evidence could render such trials unacceptable. Second, it raised questions about what ethical obligations the FDA has to patients who participate in these studies. Finally, it highlighted a potential FDA role in ensuring that institutional review boards (IRBs) are completely informed in their efforts to protect study participants. Although major deficien-

cies with the TIDE consent form were identified by some FDA scientists and, later, by the IOM committee (Table 1),[4,9] the TIDE investigators countered that it had been approved by "480 ethics committees and IRBs."[14] However, the language of the consent form, the trial design, and the materials supporting the justification of the trial raised a question for the IOM committee about whether these bodies adequately understood the nature of the evidence that gave rise to the trial. The IOM committee proposed a framework for evaluating the ethics of FDA-required postmarketing research[15] and made a number of ethics findings and recommendations.[4]

ETHICAL RESPONSIBILITIES OF THE FDA

The IOM committee began by noting that the public health mission of the FDA gives rise to potentially competing ethical obligations "to protect the public's health by having strong science on which to base regulatory decisions" and "to protect participants in research that it requires."[4] Requiring a postmarketing study is an ethical decision, reflecting a weighing of these values.

The committee described the conditions that must be present to justify a decision to require a postmarketing study. The FDA should require postmarketing research only when, first, the uncertainty about the benefit–risk balance of a drug is so great that a responsible decision about its regulatory status cannot be made on the basis of existing evidence; second, the research will reduce this uncertainty; third, the FDA will use the research results expeditiously to make a regulatory decision; and fourth, sufficient protections for research participants can be ensured.

The committee argued that when the FDA requires a postmarketing study, it assumes a measure of ethical responsibility for the welfare of the study participants; exercise of that responsibility cannot be handed off to contractors or the industry sponsor. The responsibility is particularly strong when the patients' treatment is determined by the study, such as in a randomized trial, linking any adverse outcomes directly to a regulatory decision to require a study of that type. This determination led to one of the most important recommendations from the IOM committee: the responsibilities of the FDA to research participants mean that it should mandate a randomized design only if the FDA "has concluded that an observational study could not provide the necessary information [to help answer the important public health question at issue], that an RCT [randomized, controlled trial] is likely to generate the information within the necessary timeframe, and that the necessary RCT is ethically acceptable." This recommendation comports with but adds some further conditions to the current legal authority of the FDA under the FDA Amendments Act of 2007, which empowers the agency to require a randomized trial if it cannot obtain the data it needs from an observational study.[1]

In light of the critiques of the TIDE trial as inherently unethical, the committee addressed the justifiability of trials in which participants may encounter a net increase in risk, as compared with ordinary clinical care, but no realistic prospect of personal benefit. It argued that such trials can be justified only if they are necessary to answer a critically important public health question, if the potential risk is accept-

Table 1. Major Deficiencies in the Informed-Consent Form for the TIDE Trial.*

Consent Element	Specific Deficiencies
Inadequate explanation of the purpose of research	Did not clearly explain that the purpose of the study was to definitively establish that rosiglitazone involved a significantly higher risk of serious harms than pioglitazone
	Title included minor intervention (vitamin D) whose effects were not a subject of FDA concern
Inadequate explanation of the risks of research participation	Did not convey that the FDA was concerned primarily about the safety of rosiglitazone and was requiring the sponsor to conduct the TIDE trial to investigate safety signals
	Submerged cardiovascular risks associated with rosiglitazone in a list of outcomes related to potential effects of vitamin D on cancer and bone fractures
	Characterized previous studies as having provided conflicting findings concerning the cardiovascular safety of rosiglitazone, when the weight of the evidence was against rosiglitazone
Inadequate explanation of alternatives to research participation	Did not disclose that the current clinical standard of care had moved away from the use of rosiglitazone
	Did not mention that the American Diabetes Association had recommended that rosiglitazone not be used

* Adapted from the Committee on Ethical and Scientific Issues in Studying the Safety of Approved Drugs, Institute of Medicine,[4] and Graham and Gelperin.[9] FDA denotes Food and Drug Administration, and TIDE Thiazolidinedione Intervention with Vitamin D Evaluation.

able and minimized, and if special safeguards are in place, including a highly explicit informed-consent process to ensure that patients understand that they are potentially shouldering additional risk solely to contribute to the public good.

Specific actions that the FDA should take to meet its ethical obligations include specifying the study design, title, end points, and primary analyses; identifying design features that it views as ethically and scientifically indispensable; and, for clinical trials, specifying a safety-monitoring scheme. The committee recommended that the FDA routinely communicate with IRBs about required postmarketing studies — for example, by issuing a letter to accompany IRB applications that conveys information that is material to the IRB's determination of the ethics of the research, as well as providing additional communications over the life of the study as warranted by new information about the drug or by changes in professional practice. The committee also believed that the FDA was ethically obligated to actually use the findings from required studies to make timely regulatory decisions.

INFORMED-CONSENT PROCESS FOR REQUIRED POSTMARKETING TRIALS

The IOM committee emphasized that the adequacy of the informed-consent process is only one element in the ethics of FDA-required postmarketing research. Other central, and indeed prior, features include ensuring that the selection of participants is equitable and that the level of risk to which they are exposed is acceptable. The committee also recognized, however, that there are challenges to achieving meaningful informed consent in postmarketing trials of drugs for which there is a signal indicating the possibility of drug-related harm. In such cases, there is a suspicion that the benefits of the drug may not justify its risks and often that it may have a worse benefit–risk profile than alternative drugs available to treat the same condition. The committee concluded that for postmarketing trials of such drugs, there are "heightened obligations to ensure that potential research participants understand the risks posed by study enrollment."[4] This was of particular importance for rosiglitazone, because the cardiovascular problem it appeared to cause was the same outcome that good diabetic control was supposed to improve — in other words, if this elevation in risk were real, there could be little offsetting benefit.

The committee recommended several measures to strengthen the consent process in order to maximize patients' understanding of the context in which the trial is being conducted, including what is already known about the risks associated with the drug. The report discussed both specific disclosures in the informed-consent form and special efforts that could be made to ensure adequate comprehension of complex information regarding risks (Table 2). To assist IRBs, the committee recommended that the FDA issue guidance interpreting current informed-consent regulatory requirements in the context of required postmarketing studies.

STRENGTHENING POSTMARKETING RESEARCH AND ITS GOVERNANCE

Because a true picture of the benefit–risk profile of a drug only emerges over time, two different IOM committees have stressed the need for the FDA to fully embrace a "life-cycle approach" to drug regulation, in which its obligations to protect public health are taken as seriously once a drug is on the market as they are before approval is granted.[4,16] Postmarketing regulatory oversight is assuming heightened importance as the FDA accrues additional authority to fast-track drugs for approval on the basis of more limited evidence than was previously required in order to address unmet medical needs and accelerate innovation.[17-19] This changing landscape raises several challenges for ensuring the ethical conduct of research with approved drugs and balancing societal interests in drug innovation and drug safety. We highlight two of these challenges here.

First, not all postmarketing research is ethically equivalent. The TIDE trial represented an iconic kind of postmarketing study: an FDA-required randomized trial to study a drug whose benefit–risk profile was under a cloud of suspicion and at a time when alternative treatments were available, albeit not all well studied. The risks to patients of participating in the trial probably outweighed the prospect of direct benefit. By contrast, when the FDA requires an observational study that uses previously collected data, the clinical experience of the participants is unaffected, the risks incurred are not at the behest of the FDA, and ethical concerns are largely confined to confidentiality and the right to control one's medical information.

Both of these scenarios can be distinguished

Table 2. Mechanisms for Strengthening the Informed-Consent Process for Postmarketing Drug-Safety Studies.*

Consent Element	Information to Be Conveyed
Explanation of the purpose of research	Clear explanation of why a new study is required even though the FDA already found the drug to have an acceptable benefit–risk profile
Explanation of the risks of research participation	Meaningful, balanced summary of existing evidence about the safety of the study drug Explanation of why experts deem it reasonable to ask patients to participate in the study, notwithstanding the risks involved If applicable, a statement that participants are being asked to assume a higher risk than they would be likely to encounter under the current clinical standard of care solely for the purpose of answering an important public health question Drug-risk information should go beyond a bullet-point list of possible side effects, indicating where the weight of evidence falls concerning the likelihood that serious harms will occur and the extent of current scientific uncertainty At a minimum, disclosures should include boxed warnings, a "major statement" in direct-to-consumer advertisements, salient findings from FDA advisory committees, and a summary of findings from peer-reviewed studies
Explanation of alternatives to research participation	Clear explanation of how the care that patients receive in the study may differ from the care they currently receive or would be likely to receive if they did not enroll If applicable, a statement that the current clinical standard of care has moved away from use of the study drug, and an explanation of why
Ongoing communication of relevant new information	Timely, comprehensible communications if safety signals intensify over the course of the study Recommendation that study participants consult with their treating physician to determine whether continued study participation is prudent in light of new information

* Adapted from the Committee on Ethical and Scientific Issues in Studying the Safety of Approved Drugs, Institute of Medicine.[4]

from the context in which a phase 4 trial is required as a condition of an accelerated drug approval and is initiated soon thereafter. Here, the trial requirement is not imposed because of a newly emerging concern about a drug already in clinical use but because additional evidence is needed to confirm the initial judgment that the benefits of a new drug are likely to outweigh its risks. Often, this initial judgment is based on the use of a surrogate end point for drug benefit, not on the clinical outcomes that matter most. Especially when the new drug targets an unmet medical need, it may be in the patients' best interest to take it, pending further timely research. The ensuing trial is undertaken to confirm the improvement in clinical outcomes predicted by the surrogate — a different epistemic and ethical situation than that in which substantial evidence suggests that the surrogate is misleading or that other harms might offset a known clinical benefit.

The volume of phase 4 and other research with FDA-approved drugs is increasing, not only because of the expanded authority of the FDA to require such research but also because of the growing volume of comparative-effectiveness research. In some cases, there may be no or little ethical difference between FDA-required postmarketing research and comparative-effectiveness research initiated by academic investigators. By contrast, a comparative-effectiveness study of two widely used drugs that is not occasioned by heightened concern about the risks of one drug relative to the other is markedly different, ethically, from a study required by the FDA to pursue a safety signal that is already of such concern that practice patterns are shifting, even if both studies use randomized designs.

These differences highlight the need for IRBs to be sensitive to the place where a study falls within the life cycle of a drug and to the reason for the research. Depending on who is initiating the research, for what reasons, and when, the same study design may have very different ramifications for the benefit–risk balance of the study and what patients need to know in order to provide meaningful informed consent. Trials that may be regarded as unethical late in the life cycle because of accumulated evidence can be much easier to initiate earlier if the need for additional research is anticipated and planned at the time of initial approval. In the case of rosiglitazone, this need could have been anticipated from preapproval data showing an adverse

effect on serum lipids as well as the use of a surrogate end point (glycemic control) for a first-in-class drug.[5,20]

Second, the experience with rosiglitazone underscored the fragility of our current system of discovering risks associated with drugs. This system relies heavily on drug sponsors and FDA scientists to conduct safety analyses on the basis of data from clinical trials, some or all of which are not publicly available, and to release findings to the public. It has been shown repeatedly that the published record can misrepresent evidence known to the FDA.[21,22] In the case of rosiglitazone, scientists from GlaxoSmithKline and the FDA had information from 42 clinical trials, of which only 7 were published and the others were inaccessible. Triggered by concerns expressed by the World Health Organization in 2006, GlaxoSmithKline conducted and shared with the FDA a meta-analysis of the safety of rosiglitazone that used these data, confirming a possibly elevated risk of ischemic events, but neither these results nor the primary trial results were shared with the public until an unrelated court settlement forced GlaxoSmithKline to release its complete clinical-trial data.[23] This access led to the published meta-analysis by independent researchers that made these data and concerns public in 2007.[5]

It is often the work of independent scientists that has highlighted critical safety problems with approved drugs.[5,24-29] Yet currently, data from premarketing studies that are submitted as part of a new drug application or a supplemental new drug application are largely shielded from release to external scientists and the public owing to concerns about a competitive disadvantage to drug sponsors.[30,31] The IOM committee stopped short of calling on the FDA to increase public access to such data but recommended that the agency initiate a process to determine ways to "appropriately balance public health, privacy, and proprietary interests to facilitate disclosure" of relevant data.[4] Greater transparency would better equip independent scientists to investigate early safety signals.[31] Consideration should be given to making drug-safety data from clinical trials available to the public on request once the FDA has reached a decision regarding a new drug application or a supplemental new drug application or once the manufacturer has abandoned the application, unless the manufacturer can articulate a persuasive reason why it would result in competitive harm and the FDA determines that this harm outweighs the public health benefits of releasing the information.

CONCLUSIONS

The experience with rosiglitazone and the TIDE trial offers a lesson in how our current approach to the oversight of drug-safety and postmarketing research can fail both the public and the research participants. Although terminating the TIDE trial was justifiable, it left regulators with highly suggestive but nondefinitive data on the relative safety of rosiglitazone and the closest clinical alternative, pioglitazone.[32]

Reactive policymaking is tempting but problematic. The history of regulation of human subjects research suggests that rules that are "born in scandal and reared in protectionism"[33] often fall short of providing meaningful protections to research participants and that, once adopted, regulations can ossify and become difficult to dislodge. Nevertheless, the IOM committee's report makes a number of actionable recommendations that the FDA can implement under its existing authority.[34] In addition, appointment of an independent ethics advisory board would strengthen the decision making of the FDA as it confronts emerging ethical challenges — both those arising from required postmarketing trials and those stemming from powerful new drug surveillance systems, such as the FDA's Sentinel Initiative. As the pace of the translation of discoveries from bench to bedside continues to intensify, so too does the imperative for thoughtful ethical governance throughout the life cycle of a drug.

The views expressed in this article are those of the authors and, except where noted, do not represent the official position of the Institute of Medicine or of the committee that produced the report discussed in this article.

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From the Department of Health Policy and Management, Harvard School of Public Health, Boston (M.M.M.); the Departments of Medicine and Health Research and Policy, Stanford University School of Medicine, Stanford, CA (S.N.G.); and the Berman Institute of Bioethics, Johns Hopkins University, Baltimore (R.R.F.).

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